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A pilot study of dimethyl fumarate in pulmonary arterial hypertension associated with systemic sclerosis

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Abstract

Introduction: Given the poor treatment options for pulmonary arterial hypertension–associated systemic sclerosis patients, we sought to determine clinical safety and efficacy of dimethyl fumarate, an Nrf2 agonist, and the effects on biomarkers of oxidative stress on pulmonary arterial hypertension–associated systemic sclerosis in an exploratory interventional clinical trial.

Objectives: The primary objectives were to assess the safety and efficacy of treatment with dimethyl fumarate in patients with pulmonary arterial hypertension–associated systemic sclerosis.

Methods: This was an investigator-initiated, double-blind, randomized, placebo-controlled trial conducted at two sites in the United States. The primary safety endpoint was the incidence of serious adverse events and all adverse events in dimethyl fumarate compared to placebo-treated patients. The primary efficacy endpoint was the change in 6-min walk distance from baseline to the end of treatment at Week 24 in dimethyl fumarate compared to placebo-treated patients.

Results: Six participants were randomized to either placebo (n = 2) or dimethyl fumarate (n = 4). Baseline demographics were similar in both groups. A total of 25 adverse events occurred in 6 subjects, with 14 adverse events (56.0%) having occurred in dimethyl fumarate-treated subjects. Three occurrences were identified as nausea adverse events, and two participants withdrew due to nausea. One participant in the placebo group was withdrawn after a hospitalization serious adverse event due to worsening of heart failure and shortness of breath secondary to anemia. One participant in each group completed protocol. Subjects in the dimethyl fumarate-treated group showed a non-significant reduced decline in 6-min walk distance (relative mean change of −7.07%) from baseline to Week 24 as compared to placebo-treated subjects (relative mean change of −14.97%).

Conclusion: Patients treated for pulmonary arterial hypertension–associated systemic sclerosis with 2- and 3-drug regimens, as is now typical for these patients, tolerate dimethyl fumarate poorly. Our small sample size did not provide power to suggest efficacy. We suggest that Nrf2 is still a valid therapeutic target for future trials, using better tolerated Nrf2 agonists.

Keywords

DMF, dimethyl fumarate, SSc-PAH, systemic sclerosis, pulmonary arterial hypertension, SSc, PAH, ILD, clinical trial, Nrf2 agonist

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Introduction

Systemic sclerosis (SSc) is an autoimmune disease characterized by fibrosis and vasculopathy of various internal organs. Interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) are common and serious complications in SSc patients. Pulmonary arterial hypertension–associated systemic sclerosis (SSc-PAH) is particularly difficult to manage, with a median 4-year mortality rate following diagnosis.[1] Given the poor treatment options for SSc-PAH patients, who respond suboptimally to approved PAH therapies compared to other subgroups of PAH patients, new therapies are urgently needed.[2]

While the etiology of SSc is unknown, one attractive hypothesis is that disease is driven by excessive oxidative stress.[3,4] Notably, increased levels of markers of DNA and lipid oxidation are present in the blood and urine of SSc patients.[5–8] This is the first study in PAH or SSc-PAH to examine whether blocking observed changes in oxidative stress improves markers of oxidative stress and clinical disease.

Dimethyl fumarate (DMF) is a reformulation of Fumiderm, an orally administered mixture of fumarate esters that has been used since 1994 to treat psoriasis patients in Germany and has been approved in the United States to treat multiple sclerosis. Pre-clinical data have shown the potential for DMF to affect both oxidative stress and inflammatory pathways. As both of these pathways appear key in PAH and SSc-PAH pathogenesis, we hypothesized that this is a particularly likely drug to show efficacy in SSc-PAH. In addition to being best known for its effect on Nrf2 (Nuclear factor E2-related factor 2) to initiate transcription of phase II detoxification enzymes and combat oxidative damage, DMF has also been shown to inhibit production of inflammatory mediators such as tumor necrosis factor (TNF) and interleukin (IL)-6, ameliorating oxidative stress through increasing the activity of System Xc protein, and suppressing macrophages by HCAR2 (Hydroxycarboxylic Acid Receptor 2) activation.[9–14] While DMF has an excellent safety profile, it also has common, non-serious side effects, namely flushing and gastrointestinal (GI) adverse effects. We sought to determine clinical safety and efficacy of DMF and the effects on biomarkers of oxidative stress on SSc-PAH in an exploratory interventional clinical trial as first steps to enabling larger, controlled studies.

Methods

Protocol

This was an investigator-initiated, double-blind, randomized, placebo-controlled trial conducted at two sites in the United States. The trial consisted of a screening phase ($\leq$4 weeks), 24-week treatment phase, and 12-week safety follow-up. Patients between 18 and 80 years of age were enrolled, fulfilling American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for either limited or diffuse SSc as well as World Health Organization (WHO) Group 1 PAH-associated SSc (SSc-PAH) with WHO functional Class II or III. Other inclusion criteria included a screening 6-min walk distance (6MWD) between 150 and 450 m, and a right heart catheterization showing pulmonary arterial hypertension (PAH) (mPAP $\geq$ 25 mmHg and pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure $\leq$ 15 mm Hg) and either pulmonary vascular resistance $\geq$ 240 dynes/cm^{-5} (3 Wood units) within 3 months of study entry and no change in therapy since that catheterization, or a pulmonary vascular resistance of $\geq$ 400 dynes/cm^{-5} (5 Wood units) within 12 months of study entry. Patients with moderate or severe ILD as characterized by a forced vital capacity (FVC) of $<$70% predicted were excluded, except if FVC of 60% to 70% predicted and the most recent standard of care HRCT showed only mild ILD, or if FVC of 50% to 60% predicted and the most recent standard of care high resolution computerized tomography (HRCT) showed no ILD. None of the enrolled patients' echocardiograms showed evidence of left heart disease. Written informed consent was obtained from all patients prior to study entry. Ethical approval was obtained from the Institutional Review Board at the University of Pittsburgh before the study commenced.

Dosing regimen

Patients were randomly assigned to DMF or placebo to be self-administered orally following a titration schedule reaching a minimum of 120 mg DMF or placebo twice a day by the start of week 8 (Figure 1). In the first week of the study, the subject received 120 mg DMF tablets or similar-appearing placebo tablets to be taken once per day. After the first week, subjects were instructed to take one, 120 mg tablet twice per day for the following 2 weeks. For the next month, weeks 4 through 8, the subject was instructed to take 120 mg every morning and 240 mg every evening. At weeks 8 through 24, the subject entered the maintenance phase and was instructed to take 240 mg twice a day. If unable to tolerate the maximum dose of 240 mg twice a day, the subject could continue 120 mg twice daily or the highest tolerated dose for the remainder of the maintenance period. Missed doses were instructed to not be made up, and the next dose to be taken as scheduled.

Objectives and endpoints

The primary objectives were to assess the safety and efficacy of treatment with DMF in patients with SSc-PAH. The primary safety endpoint was the incidence of serious adverse events (SAEs) and all adverse events (AEs) in DMF compared to placebo-treated patients. The primary efficacy endpoint was the change in 6MWD from baseline to the end of treatment at Week 24 in DMF compared to placebo-treated patients.

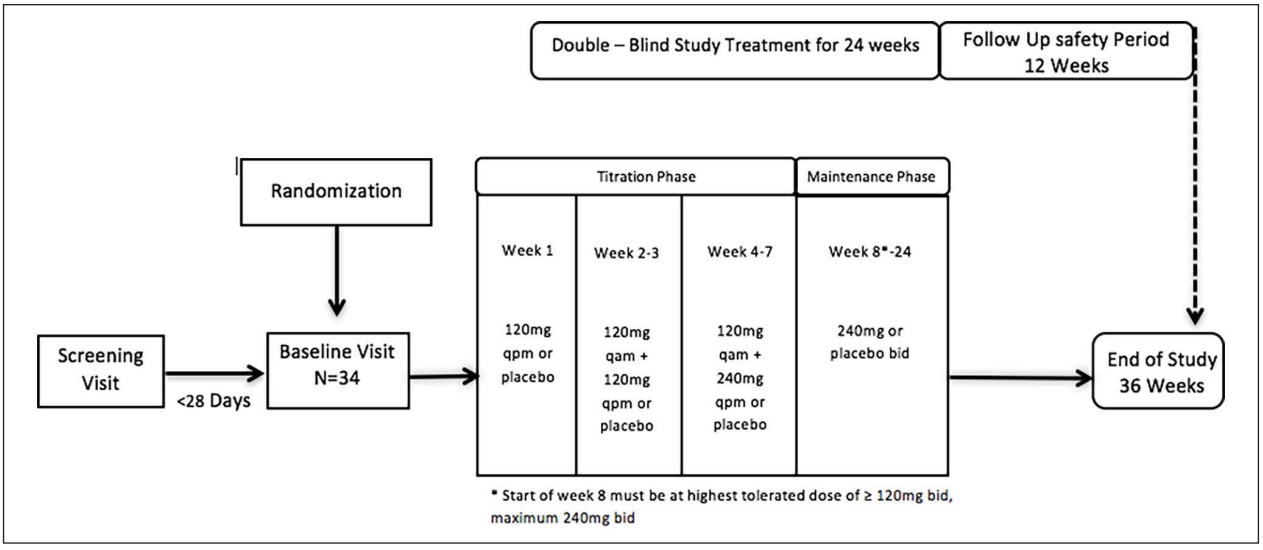

Figure 1. Study design.

Table 1. Baseline demographics of all enrolled patients.

Baseline demographics	DMF	Placebo
	n (%)	n (%)
Total enrolled:	4 (66.7%)	2 (33.3%)
Gender, n (%)		
Female	4 (100%)	2 (100%)
Ethnicity		
Hispanic or Latino	0 (0%)	0 (0%)
Not Hispanic or Latino	4 (100%)	2 (100%)
Race		
African-American	0 (0%)	1 (50%)
Caucasian	4 (100%)	1 (50%)
Age in years		
Median (mean)	66 (61.5)	72 (72)
Range	45–69	70–74

DMF: dimethyl fumarate.

Results

Study patients

Six participants were randomized to either placebo (n=2) or DMF (n=4), and the trial was stopped in November 2019 due to slow recruitment and withdrawal of recruited patients, further explained in this section. Baseline demographics were similar between DMF-treated and placebo-treated groups (Table 1).

AEs

A total of 25 AEs occurred in 6 subjects. In total, 11 AEs of the 25 (44.0%) occurred in placebo-treated subjects (Table 2). Totally, 10 of the 11 occurrences (90.9%) were determined to be possibly or probably related to the intervention, 14 AEs of the 25 (56.0%) occurred in DMF-treated subjects, 6 of the 14 occurrences (42.9%) were determined to be possibly or probably related to the intervention, and 3 of these 6 occurrences were identified as nausea AEs. There was one SAE that occurred in the placebo group, as described below.

DMF treatment has been commonly shown to be associated with GI reactions such as nausea, vomiting, diarrhea, and abdominal pain. All participants were instructed to take the study medication with food high in fat, such as peanut butter or full-fat yogurt, to better tolerate these side effects. The protocol was also modified after three subjects exhibited symptoms to slow the titration schedule and also allow subjects to remain on the highest tolerated maintenance dose (with a minimum of 120 mg BID) if 240 mg BID was not tolerated by week 8 at Visit 2. The subjects who reported GI-related side effects were treated with concomitant medications per principal investigator discretion.

Despite these efforts, four of the six participants were withdrawn from the study. Two subjects in the DMF-treated group withdrew consent before Visit 2 due to GI-related side effects experienced during the titration phase. One other participant in the DMF-treated group withdrew at Visit 4 due to meeting the stopping rule of low absolute lymphocyte count (<0.5 L) at two visits. One participant in the placebo group was withdrawn after a hospitalization SAE due to worsening of heart failure and shortness of breath secondary to anemia. One participant in each group completed protocol.

Change in 6MWD

The primary efficacy endpoint was change from baseline to Week 24 (end of study treatment phase) in 6MWD. Data depict the mean change (%) at each study visit from

Table 2. Related adverse events reported.

	DMF (n = 4)			Placebo (n = 2)	
	Total #	% Reported		Total #	% Reported
Diarrhea	1	25.0	Anemia	1	50.0
Nausea	3	75.0	Heart failure	1	50.0
Vomiting	1	25.0	Blurred vision	1	50.0
CD4 lymphocytes decreased	1	25.0	Bloating	1	50.0
			Flatulence	1	50.0
			Non-cardiac chest pain	1	50.0
			Joint effusion	1	50.0
			Headache	1	50.0
			Dyspnea	1	50.0
			Pruritus	1	50.0

DMF: dimethyl fumarate.

baseline in both treatment groups (Supplementary Materials, Figure 1S). Data points are labeled with the number of subjects continuing protocol at the specified time points while utilizing the Last Observation Carried Forward of withdrawn subjects. Subjects in the DMF-treated group showed a non-statistically significance trend toward a reduced decline in 6MWD with a relative mean change of −7.07% from baseline to Week 24 as compared to placebo-treated subjects, who show a relative mean change of −14.97%.

Discussion

Given the early study termination due to low recruitment, no definitive conclusions can be drawn. The major report of this trial is that patients treated for SSc-PAH with 2- and 3-drug regimens, as is now typical for these patients, tolerate DMF poorly. Nausea in many cases was severe. Although a well-described side effect of DMF, nausea is generally tolerable with dose titration, dietary modifications, and anti-emetic medications.[15] In addition, many patients were lymphopenic at study entry as has been described,[16] one patient developing severe lymphopenia during the study, requiring study drug discontinuation as a risk factor for progressive multifocal leukoencephalopathy. Although DMF patients showed a small trend toward improvement in their 6MWD, our small sample size did not provide power to suggest efficacy.

Pre-clinical data showing the potential for DMF to affect markers of oxidative stress and inflammation made DMF a strong candidate as a breakthrough treatment for SSc-PAH. As DMF is poorly tolerated in this patient population, we suggest that Nrf2 is still a valid therapeutic target for future trials. Bardoxolone methyl, another Nrf2 agonist, has demonstrated anti-inflammatory, anti-proliferative, and anti-fibrotic effects and continues to be investigated in patients with PAH, although efficacy and safety results have yet to be reported.[17] The involvement of the Nrf2 pathway in respiratory, cardiovascular, and autoimmune diseases and its potential as a therapeutic target remain promising.[18] Multiple Nrf2 agonists are currently in pre-clinical and clinical development, providing other potential alternatives to consider as therapies for SSc-PAH in the future.[19]

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Declaration of conflicting interests

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